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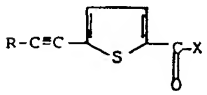
C2C

(54) Thiophene derivatives

(57) Compounds of formula I



(I)

[wherein
R represents a C_{1-16} alkyl group; and
X represents a group of formula $-NR_1OH$, $-NH(CH_2)_nOH$, $-NHNHCOR_1$ or $-NHNHCONH_2$ (in which R_1 represents a C_{1-3} alkyl group and n is from 1 to 3)] and salts thereof, exhibit *anti-inflammatory activity*. Precursors of the above amides are of formula I but in which X is halogen.

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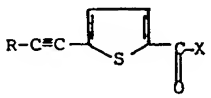
SPECIFICATION

Chemical compounds

This invention relates to new thiophenecarboxamide derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention there are provided compounds of general formula I



(I)

[wherein

R represents a C_{1-16} alkyl group; and

X represents a group of formula $-NR_1OH$, $-NH(CH_2)_nOH$, $-NHNHCOR_1$ or $-NHNHCONH_2$ (in which R_1 represents a C_{1-3} alkyl group and n is an integer from 1 to 3)] and salts thereof.

In general formula I R represents a methyl or ethyl group, or a straight-chained or branched propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl or hexadecyl group; R_1 represents a methyl, ethyl, n-propyl or isopropyl group; and n represents the integer 1, 2 or 3.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula I and physiologically acceptable salts thereof.

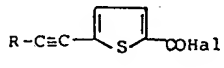
Preferred compounds according to the invention include those compounds of formula I and salts thereof wherein R represents a C_{1-10} alkyl group and X represents a group of formula $-NR_1OH$ (in which R_1 is as hereinbefore defined); those compounds of formula I and salts thereof wherein R represents a C_{1-10} alkyl group and X represents a group of formula $NH(CH_2)_nOH$ (in which n represents an integer from 1 to 3), those compounds of formula I and salts thereof wherein R represents a C_{1-10} alkyl group and X represents a group of formula $-NHNHCOR_1$ (in which R_1 is as hereinbefore defined); and those compounds of formula I and salts thereof wherein R represents a C_{1-10} alkyl group and X represents a group of formula $-NHNHCONH_2$.

Particularly preferred compounds according to the invention are as follows:

5-(1-decynyl)-N-hydroxy-N-methyl-2-thiophenecarboxamide;
5-(1-decynyl)-N-(2-hydroxyethyl)-2-thiophenecarboxamide;
N'-acetyl-5-(1-decynyl)-2-thiophenecarbohydrazide;
4-[5-(1-decynyl)-2-thenoyl]-semicarbazide;
and salts thereof.

The compounds according to the invention may, for example, be prepared by the following process, which process constitutes a further feature of the present invention:

Reaction of a compound of general formula II



(II)

(wherein R is as hereinbefore defined; and Hal represents a halogen atom, preferably a chlorine atom) with a compound of general formula

H–X

(wherein X is as hereinbefore defined).

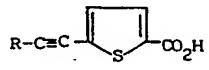
The reaction is conveniently carried out in the presence of a suitable organic solvent. In particular, when X represents a group of formula $-NR_1OH$ $-NHNHCOR_1$ or $-NHNHCONH_2$ (in which R_1 is as hereinbefore defined) the reaction is preferably carried out in the presence of an ether (including a cyclic ether) solvent such as, for example, tetrahydrofuran. Similarly, when X represents a group of formula $-NH(CH_2)_nOH$ (in which n is as hereinbefore defined) the reaction is preferably carried out in a chlorinated organic solvent such as, for example, dichloromethane.

The compounds of formula I obtained from the process according to the invention may subsequently, if desired, be converted into salts thereof, particularly physiologically acceptable salts thereof, for example by conventional methods. Such salts may be prepared *in situ* in the reaction mixture without the necessity for intermediate isolation of the compounds of formula I themselves. Conversely the salts of the compounds of formula I obtained may, if desired, subsequently be converted into compounds of formula I or into further salts thereof.

The compounds of formula II, when they are not already known, may be prepared by the

following process, which process constitutes a still further feature of the present invention:

Reaction of a compound of formula III

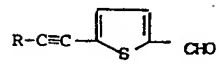


(III)

(wherein R is as hereinbefore defined) with a halogenating agent, e.g. a chlorinating agent such as, for example, oxalyl chloride.

The reaction is conveniently carried out in the presence of a dipolar aprotic solvent, e.g. dimethylformamide, and an aromatic organic solvent such as, for example, benzene, toluene or xylene.

The compound of formula III may conveniently be prepared by treating a compound of formula IV

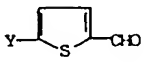


(IV)

(wherein R is as hereinbefore defined) with an oxidising agent.

A suitable oxidising agent for carrying out the above process would, for example, be silver nitrate in the presence of a base such as, for example, sodium hydroxide. In this case, the oxidation reaction is conveniently carried out in the presence of a suitable solvent such as, for example, an aqueous solution of a lower alkanol.

The compound of formula IV may conveniently be prepared by reacting a compound of formula V



(V)

(wherein Y represents a halogen atom, preferably a bromine atom) with a compound of formula VI

$$R-C\equiv CH \qquad (VI)$$

(wherein R is as hereinbefore defined) in the presence of a palladium(II) salt, a triarylphosphine and a copper(I) salt catalyst in an excess quantity of a tertiary amine/solvent mixture. A preferred system would, for example, be palladium(II) acetate, triphenylphosphine and copper(I) iodide in the presence of triethylamine/dichloromethane.

As mentioned earlier, the compounds according to the invention possess interesting pharmacological properties. In particular, they have been tested in respect of their activity as inhibitors of the synthesis of eicosanoids by guinea pig peritoneal neutrophils following the addition of [^{14}C]-arachidonic acid and calcium ionophore, using a modification of the method published by Harvey, J. and Osborne, D.J. in *J. Pharmacol. Methods, 9* [2], 147–155 (1983). The compounds according to the invention selectively inhibit 5-lipoxygenase product (5-HETE) synthesis. These data are exhibited in the following Table:

Example	IC_{50} (μM)
1	0.028
2	7.1
3	6.3

Such compounds are thus of use in the treatment of inflammatory diseases (including bronchial asthma, rheumatoid arthritis, psoriasis and collitis), immuno-regulatory diseases and cardiovascular diseases, and in other syndromes in which leukotrienes (the products of the 5-lipoxygenase system) may be implicated. Thus, the present invention provides compounds of formula I and physiologically acceptable salts thereof for use in therapy.

According to a yet further feature of the present invention there are provided pharmaceutical compositions containing, as active ingredient, at least one compound of formula I as hereinbefore defined or a physiologically acceptable salt thereof in association with one or more pharmaceutical carriers and/or excipients.

For pharmaceutical administration the compounds of general formula I and their physiologically acceptable salts may be incorporated into conventional preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal, parenteral or topical administration.

Preferred forms include, for example, plain tablets, coated tablets, capsules, granules, ampoules, suppositories and solutions, e.g. for injection.

The active ingredient(s) may be used in conjunction with excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable doage units for administration to adults contain from 10 to 500 mg of active ingredient. The total daily dosage, which may be varied according to the compound used, the subject treated and the complaint concerned, may, for example, be from 50 to 250 mg.

According to a still further feature of the present invention, there is provided a method for the treatment of a patient suffering from, or susceptible to, inflammatory, immuno-regulatory, cardiovascular or related diseases which comprises administering to the said patient an effective amount of a compound of formula I as hereinbefore defined or a physiologically acceptable salt thereof.

The following non-limiting Examples serve to illustrate the present invention more fully.

Preparation A: 5-(1-Decynyl)-2-thiophenecarbonyl chloride Step (a):

A solution of 5-bromo-2-thiophenecarboxaldehyde (19.1 g, 0.1 mol) in a mixture of dry dichloromethane (100 ml) and dry triethylamine (100 ml) was submitted to partial vacuum under dry nitrogen for a few minutes. Triphenylphosphine (0.78 g, 3 mmol), palladium(II) acetate (0.23 g, 1 mmol), copper(I) iodide (76 mg, 0.4 mmol) and 1-decyne (17.3 g, 0.125 mol) were then added, and the mixture was heated under reflux for 24 hr. After filtering through glass wool, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (200 ml). The solution was washed with ice-cold aqueous hydrochloric acid (1N, 100 ml) and water, and was then evaporated to dryness to yield a residue (28.7 g) which was used directly in the next step.

Step (b):

Sodium hydroxide (16.0 g, 0.4 mol) was added to a rapidly stirred solution of silver nitrate (37.0 g, 0.22 mol) in water (250 ml). A solution of the residue from the previous step (28.7 g) in ethanol (250 ml) was rapidly added dropwise, and the mixture was stirred overnight at room temperature, then for 1 hr under reflux. After filtering, the solvent was removed under reduced pressure and the residue was washed with ether. Ice-cold aqueous hydrochloric acid (1N) was added, and the mixture was extracted with ether. The combined ether extracts were washed with water and concentrated under reduced pressure, to yield 5-(1-decynyl)-2-thiphenecarboxylic acid (13.7 g, 52%) as yellow crystals, m.p. 86–9°C

Found: C, 68.21; H, 7.61; S, 11.97%.
$C_{15}H_{20}O_2S$ requires C, 68.15; H, 7.63; S, 12.3 %.

ν_{max}: 2840 (br), 2220, 1660 (br) cm^{-1}.

Step (c):

To a stirred mixture of the acid obtained from the previous step (4.0 g, 15 mmol) and dry dimethylformamide (1.1 g, 15 mmol) in dry benzene (40 ml), under nitrogen and in an ice-bath, was added oxalyl chloride (3.8 mmol) at a rate such that the temperature did not rise above 6°C. After an additional 1 hr in the ice-bath the benzene was decanted from a yellow oil which was washed with petroleum ether. The combined solvents were evaporated to dryness under reduced pressure to give a pale yellow oil (4.3 g), ν_{max} 2210 and 1740 cm^{-1}, which was used without further purification.

Example 1: 5-(1-Decynyl)-N-hydroxy-N-methyl-2-thiophenecarboxamide

To a stirred solution of the acid chloride obtained from Preparation A (4.3 g, 15 mmol) in tetrahydrofuran (48 ml), in an ice-bath, was added dropwise a solution of N-methylhydroxylamine hydrochloride (1.5 g, 18 mmol) in water (24 ml), keeping the temperature at approximately 10°C. After standing the reaction mixture at 0°C until starting material had disappeared (tlc), the solvent was removed under reduced pressure and the residue was extracted with petroleum ether. The extract was washed with water and the solvent was evaporated to give the *amide*

(2.55 g, 58%) as colourless crystals, m.p. 56–8°C.

Found: C, 65.57; H, 7.84; N, 4.76; S, 10.96%.
$C_{16}H_{23}NO_2S$ requires C, 65.49; H, 7.90; N, 4.77; S, 10.93%.

ν_{max}: 3100 (br), 2850 (br), 2210, 1570 (br) cm^{-1}.
τ ($CDCl_3$): 1.01 (1H, br s, NOH), 2.39 (1H, d: J=5 Hz, thiophene H), 2.99 (1H, d: J=5 Hz, thiophene H), 6.70 (3H, s, NCH_3), 7.55 (2H, t: J=6 Hz, $C{\equiv}CCH_2$), 8.25–8.48 (2H, m, CH_2CH_3), 8.45–8.85 (10H, m, $5\times CH_2$), 9.10 (3H, t: J=6 Hz, CH_2CH_3).

Example 2: 4-[5-(1-Decynyl)-2-thenoyl]-semicarbazide
Using the procedure described in Example 1, the acid chloride obtained from Preparation A was reacted with semicarbazide hydrochloride to give the *thenoyl semicarbazide* (37%) as an off-white solid, m.p. 158–60°C (from ethanol).

Found: C, 59.68; H, 7.23; N, 13.08%.
$C_{16}H_{23}N_3O_2S$ requires C, 57.79; H, 7.21; N, 13.07%.

ν_{max}: 3430, 3300, 2910, 2840, 1670 and 1640 cm^{-1}.

Example 3: N'-Acetyl-5-(1-decynyl)-2-thiophenecarbohydrazide
Using the procedure described in Example 1, the acid chloride obtained from Preparation A was reacted with acethydrazide to give the *carbohydrazide* (76%) as an off-white solid, m.p. 119–24°C (from ethyl acetate/petroleum ether).

Found: C, 63.90; H, 7.60; N, 8.76%.
$C_{17}H_{24}N_2O_2S$ requires C, 63.72; H, 7.55; N, 8.74%.

ν_{max}: 3220, 2920, 2840, 2220 and 1675 cm^{-1}.

Example 4: 5-(1-Decynyl)-N-(2-hydroxyethyl)-2-thiophenecarboxamide
A solution of the acid chloride obtained from Preparation A (4.1 g, 14.6 mmol) in dry dichloromethane (20 ml) was added dropwise to a solution of ethanolamine (2.7 g, 43.9 mmol) in dry dichloromethane (14 ml), keeping the temperature below 5°C. After the reaction mixture had been stirred overnight at room temperature the solvent was removed under reduced pressure, water was added and the residue was acidified with aqueous hydrochloric acid (2N). Extraction with ether yielded the *carboxamide* (2.7 g, 60%) as colourless crystals, m.p. 91–7°C (from ether/petroleum ether).

Found: C, 66.49; H, 8.22; N, 4.55%.
$C_{17}H_{25}NO_2S$ requires C, 66.41; H, 8.20; N, 4.56%.

ν_{max}: 3290 (br), 2920, 2850 and 1620 cm^{-1}.

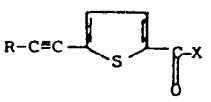
Example 5
Tablets were prepared according to the formulation:

—compound of Example 1	10 mg
—excipient q.s. for one tablet up to	200 mg

(details of the excipient : lactose, starch, talc, magnesium stearate).

CLAIMS

1. Compounds of formula I



(I)

[wherein
R represents a C_{1-16} alkyl group; and
X represents a group of formula $-NR_1OH$, $-NH(CH_2)_nOH$, $-NHNHCOR_1$ or $-NHNHCONH_2$ (in which R_1 represents a C_{1-3} alkyl group and n is an integer from 1 to 3)] and salts thereof.

2. Compounds as claimed in claim 1 wherein R represents a C_{1-10} alkyl group and X represents a group of formula $-NR_1OH$ (in which R_1 is as defined in claim 1), $-NH(CH_2)_nOH$ (in which n

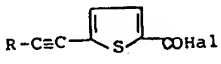
represents an integer from 1 to 3), $-NHNHCOR_1$ (in which R_1 is as defined in claim 1) or $-NHNHCONH_2$.

3. 5-(1-Decynyl)-N-hydroxy-N-methyl-2-thiophenecarboxamide;
5-(1-decynyl)-N-(2-hydroxyethyl)-2-thiophenecarboxamide;
N'-acetyl-5-(1-decynyl)-2-thiophenecarbohydrazide;
4-[5-(1-decynyl)-2-thenoyl]-semicarbazide;
and salts thereof.

4. Physiologically acceptable salts of compounds of formula I as defined in claim 1.

5. Compounds as claimed in claim 1 as herein specifically disclosed in any one of Examples 1 to 4.

6. A process for the preparation of a compound of formula I as defined in claim 1 which comprises reacting a compound of general formula II



(II)

(wherein R is as defined in claim 1; and Hal represents a halogen atom) with a compound of general formula

H–X

(wherein X is as defined in claim 1).

7. A process as claimed in claim 6 wherein the compound of formula II, Hal represents a chlorine atom.

8. A process as claimed in claim 6 or claim 7 wherein the reaction between the compound of formula II and the compound of formula H–X is effected in an ether or chlorinated organic solvent.

9. A process as claimed in any one of claims 6 to 8 wherein a compound of formula I initially obtained is subsequently converted into a salt thereof and/or a salt of a compound of formula I is subsequently converted into a compound of formula I.

10. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

11. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 4.

12. Compounds of formula I as defined in claim 1 and salts thereof whenever prepared by a process as defined in any one of claims 6 to 11.

13. Compounds as claimed in any one of claims 1 to 5 for use in therapy.

14. The use of a compound as claimed in any one of claims 1 to 5 for the manufacture of an anti-inflammatory medicament.

15. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically acceptable salt thereof in association with a pharmaceutical carrier and/or excipient.

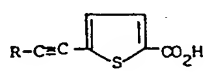
16. Compositions as claimed in claim 15 wherein the active ingredient comprises a compound as defined in any one of claims 2 to 5.

17. Compositions as claimed in claim 15 or 16 in the form of dosage units.

18. Compositions as claimed in claim 17 wherein each dosage unit contains from 50 to 250 mg of active ingredient.

19. Pharmaceutical compositions as claimed in claim 15 substantially as herein described.

20. A process for the preparation of a compound of formula II as defined in claim 6 which comprises reacting a compound of formula III

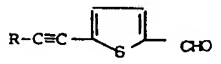


(III)

(wherein R is as defined in claim 1) with a halogenating agent.

21. A process as claimed in claim 20 wherein the halogenating agent used is oxalyl chloride.

22. A process as claimed in claim 20 or claim 21 wherein the compound of formula III is prepared by treating a compound of formula IV

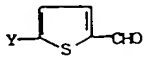


(IV)

(wherein R is as defined in claim 1) with an oxidising agent.

23. A process as claimed in claim 22 wherein the oxidising agent used is silver nitrate in the presence of a base.

24. A process as claimed in claim 22 or claim 23 wherein the compound of formula IV is prepared by reacting a compound of formula V



(V)

(wherein Y represents a halogen atom) with a compound of formula VI

$$R-C\equiv CH \qquad (VI)$$

(wherein R is as defined above) in the presence of a palladium(II) salt, a triarylphosphine and a copper(I) salt catalyst in an excess quantity of a tertiary amine/solvent mixture.

25. A process as claimed in claim 24 wherein the reaction between the compound of formula (V) and the compound of formula VI is effected in the presence of palladium(II) acetate, triphenylphosphine, copper(I) iodide and triethylamine/dichloromethane.

26. Each and every novel method, process, compound and composition herein disclosed.

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